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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STONE, CHRISTOPHER R	

ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
01/11/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No.	Applicant(s)	
	10/582,124	GREENSMITH ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER R. STONE	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed November 11, 2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of Claims

Claims 6-11 are pending and under examination. Amyotrophic lateral sclerosis (ALS) is the elected specie of neurodegenerative disease currently under examination.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cioca et al (WO 03/049692 A2) in view of Vigh et al (WO 97/16439, provided by Applicant) and Urogdi et al (WO 01/79174 A1, provided by Applicant).

Claims 6-11 are drawn to a method of treating neurodegeneration in the central nervous system, wherein the neurodegeneration is associated with ALS, comprising administering N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride.

Cioca et al teaches a method of treating ALS comprising administering compounds that induce the expression of heat shock proteins (claims 5 and 6). Cioca et al teaches that hydroxylamine derivatives, such as N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-3-caroximidoyl chloride (bimoclomol), are known heat shock protein (HSP) inducers (p. 2, lines 7-12). Cioca et al further teaches that heat shock proteins are known to be crucial for the maintenance of cell (e.g. neuronal) health and integrity in ALS (p. 2, lines, 19-23). Cioca et al does not expressly teach the instantly claimed compound, (+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate (arimoclomol, an N-oxide of bimoclomol), as the particular heat shock protein inducing hydroxylamine derivative.

Vigh et al teaches that N-oxides of N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-3-caroximidoyl chloride (bimoclomol), prepared by the N-oxidation of e.g. the

terminal pyridine group (p. 22, lines 8-10), increase the expression of heat shock proteins (p. 5, lines 11-14 and p. 27, lines 6-9 and 22-29).

Urogdi et al teaches (+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate (an N-oxide of bimoclomol, prepared by the N-oxidation of the terminal pyridine group) as a pharmaceutically useful N-oxide of N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-3-caroximidoyl chloride (p. 1, line 21 through p. 2, line 3, p. 6, lines 15-17 and p. 13, Example 5).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of the instantly claimed invention to treat neurodegeneration associated with ALS by administering (+)-R-N-[2-hydroxy-3-(1-piperidinyl)-propoxy]-pyridine-1-oxide-3-carboximidoyl chloride citrate, since the compound was known to have activity useful in the treatment of ALS, thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success.

Response to Arguments

Applicant argues that the applied references fail to enable one of ordinary skill in the art to practice the instantly claimed invention because: the pharmacological treatment of ALS was unpredictable at the time of the instantly claimed invention, the applied references do not contain working examples, the references provide no direction or guidance in the form of real-world treatment of the disease. Thus it would take undue experimentation by one of ordinary skill in the art to practice the instantly claimed invention with no reasonable expectation of success.

These arguments have been carefully considered but are found unpersuasive.

With regard to the state of the art and predictability of the pharmacological treatment of ALS at the time of the instantly claimed invention, the prior art recognized the ability of the increased expression of HSPs to treat neurodegeneration in the central nervous system, particular neurodegeneration related to ALS, as stated by Cioco et al (see also Kalmar et al and Bruening et al, previously made of record). Furthermore bimoclomol and its analogs were known to induce the expression of HSPs and provided neuroprotective activity *in vivo* (Kalmar et al, abstract and p. 87, right column). With regard to the lack of working examples in the applied references, the lack of working examples should never be the sole reasons for a determination of lack of enablement and the state of the prior art is related to the need for working examples in the specification. As noted above the art recognized the correlation between the increased expression of HSPs and neuroprotection in neurodegenerative disease, including ALS, as well as the ability of bimoclomol and its analogs to induce the expression of HSPs and provided neuroprotective activity *in vivo*. Furthermore, the prior recognizes an in vivo mouse model of ALS and the ability of the increased expression of HSPs to provide neuroprotection in said model (Bruening et al, abstract). Thus given the state of the prior art and the high level of skill in the art one of ordinary skill in the art would have been able to practice the instantly claimed method with a reasonable expectation of success given the teachings of the applied references. In the instant case the art teaches the ability of the instantly claimed compound to induce HSPs *in vivo*, the neuroprotective effect of increased HSP expression in neurodegenerative disease, and further provides a model of the disease and demonstrates the neuroprotective effect of increased HSP

expression in said model providing a reasonable degree of predictability and a reasonable expectation of success in the treatment of ALS, in contrast to the fact pattern presented in exhibit A.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER R. STONE whose telephone number is (571)270-3494. The examiner can normally be reached on Monday-Thursday, 7:30am-4:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brandon J Fetterolf/
Supervisory Patent Examiner, Art Unit 1628